Diagnosis, treatment and prophylaxis of meningitis

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Bacterial meningitis remains one of the most dreaded infections, but rapid diagnosis and early treatment can significantly reduce both the mortality and long-term neurological sequelae.

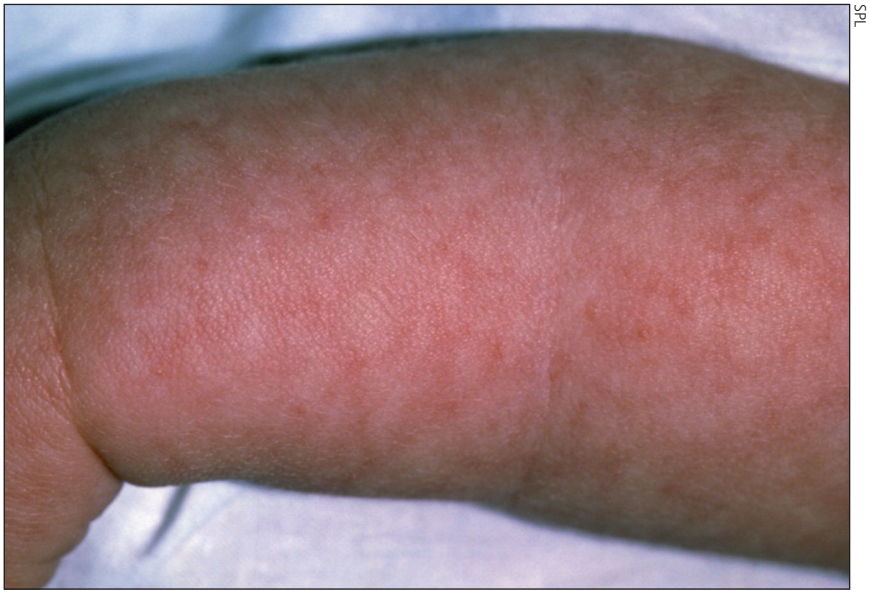
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Figure 1. Rash due viral meningitis in a baby girl; in the early stages of infection it is clinically difficult to differentiate bacterial and viral meningitis

The introduction of conjugate vaccines against many of the bacterial causes of meningitis over the last 20 years has had a dramatic impact on the epidemiology of bacterial meningitis. The use of *Haemophilus influenzae* type b (Hib) vaccine in 1992 and meningococcal serogroup C (MenC) conjugate vaccine in 1999 in the UK has resulted in the near elimination of invasive disease caused by these pathogens across all age groups through direct and indirect (herd) protection. Conjugate vaccines not only produce direct protection of immunised individuals. They also reduce nasopharyngeal carriage of the types of bacteria targeted by the vaccine, resulting in reduced transmission to other susceptible individuals. This indirect effect of conjugate vaccines is called herd protection.

The 7-valent pneumococcal vaccine (PCV7), introduced in 2006, resulted in a decline in the number of cases of pneumococcal meningitis caused by vaccine types, and the replacement of PCV7 by the 13-valent pneumococcal conjugate vaccine (PCV13) in 2010 is producing a further decline in invasive pneumococcal disease caused by vaccine serotypes. There are more than 90 serotypes of *Streptococcus pneumococcus*, which vary in their capacity to cause invasive disease. The use of pneumococcal conjugate vaccines has resulted in serotype replacement, where non-vaccine serotypes replace vaccine serotypes in the nasopharynx, and may cause invasive disease, including meningitis.

In addition to the effects of these conjugate vaccines, there has also been a decline in cases of meningococcal-meningitis due to meningococcus serogroup B (Men B) since the early 2000s. This has occurred in the absence of any vaccination and probably reflects the natural secular trends in MenB disease. However, meningococcal meningitis remains the most important cause of bacterial meningitis.

Despite the decline in the number of cases of Hib, MenC and pneumococcal meningitis, the overall annual number of cases of bacterial meningitis has remained relatively stable over the past decade, as a result of the concomitant increase in the incidence of Group B streptococcal meningitis in infants less than three months of age, and Gram-negative meningitis (*Escherichia coli* and *Klebsiella*) predominantly in the elderly.

Age	Bacterial pathogens
<1 month	Group B streptococcus, *Escherichia coli*, *Listeria monocytogenes*
1–23 months	Pneumococcus, meningococcus, Group B streptococcus, *Escherichia coli*
2–50 years	Meningococcus, pneumococcus
>50 years	Pneumococcus, meningococcus, *L. monocytogenes*
Immunocompromised	Pneumococcus, meningococcus, *L. monocytogenes* Gram-negative bacilli
Basal skull fracture	Pneumococcus, *Haemophilus influenzae*[a], Group A streptococcus

Table 1. Likely causative organism of bacterial meningitis in different age groups and in patients with underlying conditions; [a]non-typable *H. influenzae* (not covered by Hib vaccine)

Viral meningitis

Meningitis or meningoencephalitis may also be caused by a number of viruses. The number of cases of viral meningitis has increased over the last decade from 311 in 2004 to 1247 cases in 2013. The increase has been seen in all age groups, with the highest incidence in infants under three months of age. Enteroviruses are responsible for over 50 per cent of cases, especially in those under three months old. The second most common virus identified is herpes simplex virus, which causes >50 per cent of cases in adults under 45 years of age. Enteroviral meningoencephalitis shows a seasonal trend with a peak in summer and the lowest number of cases in winter. Other viral causes of meningoencephalitis do not show any seasonality.

Bacterial meningitis

Early recognition of bacterial meningitis is essential to enable antibiotics to be administered as soon as possible. The classic symptoms of fever and headache are relatively non-specific and may resemble a flu-like illness. Neck stiffness, photophobia and impaired consciousness may not be present in many young children and adults or may develop later. The patient should be carefully examined for any signs of a rash, suggestive of meningococcal meningitis or meningococcaemia. In the early stages of infection the rash may not be obvious, may be blanching or maculopapular, but usually evolves in to a non-blanching petechial or purpuric rash.

Up to 20 per cent of patients with meningococcal infection may not develop a rash or it may be an atypical maculopapular rash. A thorough medical history should be obtained, including recent travel, vaccinations, medications, past medical history and any underlying co-morbidities. Many patients with bacterial meningitis have predisposing conditions. Approximately 40 per cent of patients with pneumococcal meningitis have preceding ear, sinus or lung infections. *Haemophilus* meningitis is also commonly preceded by an upper respiratory tract infection. The age of the patient may give an indication of the likely causative organisms of community-acquired bacterial meningitis (see Table 1).

In the majority of cases of bacterial meningitis, a bacteraemia precedes the onset of meningitis with bacteria invading the central nervous system from the bloodstream. A history of previous head injury or neurosurgery should alert the clinician to the possibility of a hairline fracture of the base of the skull or cribriform plate, allowing direct access of bacteria to the cerebral spinal fluid (CSF) from the nasopharynx or orpharion. Patients with basal skull fractures are at risk of developing meningitis due to pneumococcus, *H. influenzae* (non-typable strains, not covered by Hib vaccine) and Group A streptococcus. Such defects should be identified by MRI or CCT scans.

Drug	Dose for infants <1 year	Dose for children aged 1–9 years	Dose for children ≥ 10 years and adults
Benzyl penicillin (penicillin G)	300mg	600mg	1.2g
Cefotaxime[a]	50mg/kg	50mg/kg	1g (for children ≥12 years and adults)
Chloramphenicol[b]	12.5mg/kg	12.5mg/kg	12.5mg/kg

[a]Cefotaxime (if available) should be used for patients with penicillin allergy
[b]Chloramphenicol (if available) may be used for patients with a history of an immediate hypersensitivity reaction to penicillins and cephalosporins

Table 2. Empirical antibiotic therapy to be given in cases of suspected meningococcal meningitis or meningococcal septicaemia

Treatment

In the early stages of the infection it is difficult to clinically differentiate bacterial and viral meningitis. For this reason it is essential to arrange urgent hospital admission for cases of suspected meningitis to enable CSF examination and culture to be carried out. If meningococcal meningitis or meningococcal septicaemia is suspected (presence of a non-blanching rash) benzyl penicillin should be administered before the patient is transferred to hospital, as long as this does not delay hospitalisation. Cefotaxime can be used in patients with a history of penicillin allergy, or chloramphenicol if there is a history of immediate hypersensitivity to penicillin or cephalosporins. If pneumococcal meningitis is suspected then cefotaxime should be given. Table 2 gives details of the dosages of this emergency empirical antibiotic treatment.

An accurate microbiological diagnosis is essential to ensure appropriate antimicrobial therapy. This is normally achieved by examining the cerebrospinal fluid, usually obtained by lumbar puncture. In some cases this should follow cranial imaging if there is a risk of cerebral herniation. Empirical antimicrobial treatment should be started before the lumbar puncture, if the procedure is likely to be a delayed by

Age	Dosage
<5 years	30mg/kg (up to a maximum of 125mg *stat*)
5–12 years	250mg *stat*
Adults and children >12 years	500mg
Ciprofloxacin suspension contains 250mg/ml	

Table 3. Dosage of ciprofloxacin prophylaxis for close contacts of cases of meningococcal meningitis and meningococcal septicaemia

more than 30 minutes. These agents have good activity against all of the major bacterial pathogens, except *Listeria monocytogenes*, for which amoxicillin and gentamicin are more appropriate.

Notification

Acute meningitis and meningococcal septicaemia are notifiable infections under the Health Protection (Notification) Regulations 2010. The attending registered medical practitioner (RMP) should report each case to the "Proper Officer" of the Local Authority or Health Protection Unit (HPU). The RMP should fill out a notification certificate immediately on diagnosis of a suspected notifiable disease and should not wait for laboratory confirmation of the suspected infection before notification. The certificate should be sent to the Proper Officer within three days or verbally within 24 hours if the case is considered urgent. Notification is important to enable contacts to be traced and prophylactic antibiotics given for close contacts of a suspected or proven case of meningococcal meningitis or meningococcal septicaemia.

Prophylaxis

Chemoprophylaxis should be offered to close contacts of cases of meningococcal meningitis or meningococcal septicaemia, irrespective of vaccination status, in the following categories:

(a) Those who have had prolonged close contact with the case in a household type setting during the seven days before onset of illness. Examples of such contacts would be those living and/or sleeping in the same household (including extended household), pupils in the same dormitory, boy/girlfriends, or university students sharing a kitchen in a hall of residence.

(b) Those who have had transient close contact with a case only if they have been directly exposed to large particle droplets/secretions from the respiratory tract of a case around the time of admission to hospital.

The recommended antibiotic for prophylaxis in contacts of all ages is a single oral dose of ciprofloxacin (see Table 3). Rifampicin may be used in cases of known ciprofloxacin hypersensitivity (see Table 4). Ciprofloxacin is usually not recommended in young children as it can cause induced arthropathy in juvenile animals, but studies have shown the risk in young children is very low.

Immunisation programme

In January 2013, a novel 4-component meningococcus serogroup B vaccine (4CMenB, Bexsero) was licenced by the European Medicines Agency. *In vitro* studies suggest that this vaccine could cover up to 88 per cent of the MenB strains currently circulating in the UK. The Joint Committee on Vaccination and Immunisation (JCVI) after reviewing the evidence has recommended that the DH plan to implement a 2, 4 and 12 month (2+1) immunisation programme with 4CMenB.

They also recommended removal of the three-month dose of MenC vaccine from the schedule following the introduction of 4CMenB and the implementation of an adolescent booster programme with MenACWY vaccine. This programme has the potential to reduce the burden of invasive meningococcal disease and meningococcal meningitis among those at the greatest risk of these infections.

Age	Dosage
Infants <1 year	5mg/kg twice daily for 2 days
Children 1–12 years	10mg/kg twice daily for 2 days
Children >12 years and adults	600mg twice daily for 2 days

Table 4. The dosage of prophylactic rifampicin for close contacts of meningococcal meningitis (the prophylactic regimen of *Haemophilus* meningitis is different)

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Declaration of interests

Dr Agass has none to declare. Professor Slack has served on *ad-hoc* advisory boards for Pfizer, GSK and Sanofi Pasteur. She was also formerly an employee of the Public Health England Respiratory and Vaccine Preventable Bacteria Reference Unit, which has received research funding from Pfizer and GSK.

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